An Improved and Efficient Process for the Production of Highly Pure Dexmethylphenidate Hydrochloride

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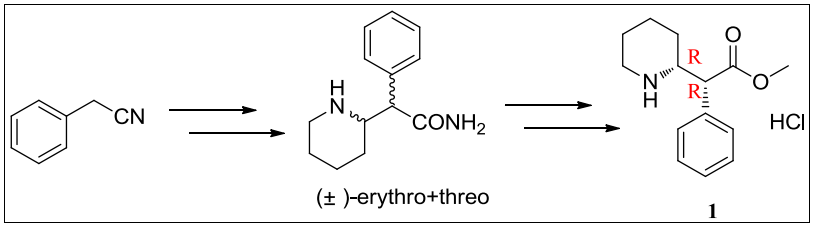


The present work describes an efficient and commercially viable process for the synthesis of dexmethylphenidate hydrochloride (**1**), a mild nervous system stimulant. The overall yield is 23% with ~99.9% purity (including seven chemical steps). Formation and control of possible impurities are also described in this report.

INTRODUCTION

Dexmethylphenidate hydrochloride ((*R*)-methyl 2-phenyl-2-((*R*)-piperidin-2-yl)acetate hydrochloride **1**; Fig. 1), a mild central nervous system stimulant, was developed and marketed for the treatment of pediatric attention deficit hyperactivity disorder by Celgene Corp (Summit, NJ) [1]. It is primarily used in its racemic form (±)-*threo*-methylphenidate hydrochloride (**2**; Fig. 1) [2]. **1** has been reported to be more active with fewer side effects than the corresponding (*2S*, *2'S*)-(-)-*threo*-isomer [3].

Several processes are reported for the preparation of dexmethylphenidate hydrochloride (**1**) [1,4], but the most preferable and convenient route for synthesis of **1** mainly involves S_NAr arylation of benzeneacetonitrile (**3**) with 2-chloropyridine (**2**), to hydrolyze the nitrile **4** and obtain the amide **5**. Catalytic reduction of **5** was then performed and afforded **6** as a mixture of *threo* and *erythro* forms. This mixture was treated with a base to epimerize the *erythro* isomer into the *threo* isomer **7**. Resolution of **7** with acid resolving agent then afforded (*2R*, *2'R*)-(+)-*threo*-isomer **8**, which was converted to the desired dexmethylphenidate hydrochloride (**1**) by treatment with concentrated sulfuric acid, methanol, and hydrochloride (Scheme 1).

Active pharmaceutical ingredients (API) can be contaminated by impurities, which may influence drug quality and safety [5]. During our process development of dexmethylphenidate hydrochloride (**1**), some impurities were formed and identified, and this represents the first identification of such. To improve the product process and quality, identification and characterization of API impurities is a regulatory requirement. Here, we report the process optimization and mechanisms for decreasing impurities in dexmethylphenidate hydrochloride.

RESULTS AND DISCUSSION

Intermediate **4** was prepared according to methods in the literature [4d] with modifications and improvements (Scheme 1). The S_NAr arylation of benzeneacetonitrile (**3**) with 2-chloropyridine (**2**) under different reaction conditions was explored. The synthetic processes for α-arylation of nitriles with different bases and solvents are reported in the literature, such as KOH/DMSO [6], tetrabutylammonium fluoride (TBAF)/NaOH/PhMe [7], sodium bis(trimethylsilyl)amide (NaHMDS)/PhMe-THF [8], and $NaNH_2$/ PhMe [4d]. In our synthetic process development of **4**, a variety of conditions were examined, as shown in Table 1. Specifically, by using NaHMDS or $NaNH_2$ as base, afforded the desired compound **4** in 50–60% isolated yield (entries 4–6). These low yields may be explained by the simultaneous formation of product along with ketone **4A** as a major impurity (Fig. 2). This impurity results from oxidative decyanation of secondary nitrile during S_NAr arylation, as proposed in

1 (±)-*threo*-methylphenidate HCl (**2**)

Figure 1. Structures of **1** and **2**.

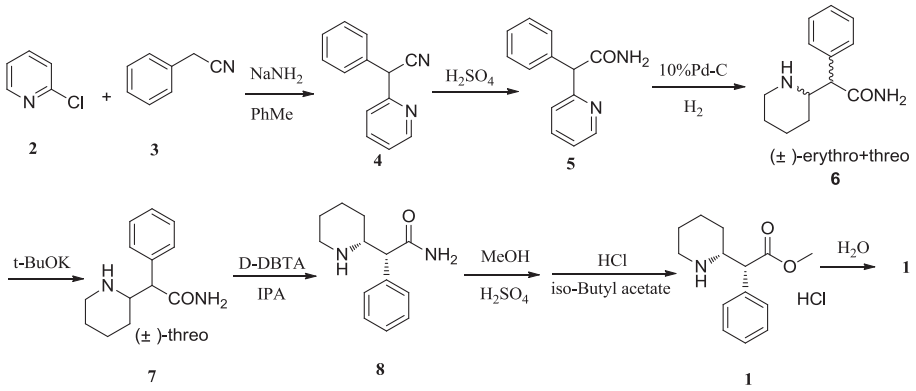
Scheme 2 [9]. Impurity **4A** is an oxidative decyanation product, so the oxygen in the solvent may be a factor. Thus, oxygen-free solvents were used to synthesize intermediate **4**, and yields were greater (Table 1, entries 7–8) compared with reactions with solvents without pretreatment (entries 4–6). The best reaction conditions among those tabulated include oxygen-free toluene as solvent and $NaNH_2$ as a base for S_NAr arylation (entries 7). Compound **4** was a light-yellow solid, and purity could be improved to $>98\%$. Impurity **4A** could be reduced to $\leq 0.1\%$ after recrystallization.

Next, the nitrile **4** was hydrolyzed using concentrated sulfuric acid to obtain the amide **5** with good yield [4d]. After compound **5** was obtained, catalytic hydrogenation conditions, such as catalysts, pressure, time, and solvents were investigated as summarized in Table 2. Various catalysts (Pt/C [6], PtO_2/C [4d], Rh/C [10], and Pd/C [4c]) have been described in the literature for this hydrogenation process. Based on price, Pd/C was chosen for further investigation. Experiments were first performed using 5% Pd/C as catalyst, under different pressures and solvents and this resulted in poor conversion even after 20 h (Table 2, entries 1–2). Compound **5** was hydrogenated using 10% Pd/C as a catalyst to give **6** in moderate to good yields (entries 3–7). Optimal reaction condition are given in entry 3. This reaction afforded the compound **6** as a mixture of *threo* and *erythro* forms, and the ratio (*threo*/*erythro*: 20/80) was established by HPLC.

With compound **6** in hand, the *threo* and *erythro* mixture was then treated with potassium tert-butoxide to epimerize the *erythro* stereoisomer into *threo* form **7** with about 80% yield and this agrees with published yields [4d].

In the next step, the resolution of (±)-threo-2-phenyl-2-(piperidin-2-yl)acetamide (**7**) was explored. Three commercially available acids (D-tartaric acid (D-TA), dibenzoyl-D-tartaric acid (D-DBTA), and ditoluoyl-D-tartaric acid(D-DTTA)) were selected and tested for resolution of **7** as shown in Table 3. Among these acids, resolution with D-DBTA in methanol, although successful, produced **8** at only 25.2% yield (entry 2). Also, the solvent had significant effects on resolution yield. Resolution with isopropyl alcohol produced

Scheme 1. Synthesis route of **1**.



2 **3** **4** **5** **6** **7** **8** **1**

Table 1

Variation of conditions for the arylation step.

Entry	Base	Solvent	HPLC (%)			
			2	**3**	**4**	**4A**
1	KOH	DMSO	30.4	32.5	10.5	15.6
2	aq. NaOH/TBAF(as phase transfer catalyst)	PhMe	44.6	47.3	1.0	0.5
3	t-BuOK	DMF	43.2	46.3	0.5	0.1
4	KHMDS	PhMe/THF	13.5	15.8	50.1	15.2
5	$NaNH_2$	PhMe	1.0	1.3	60.4	32.5
6	$NaNH_2$	PhMe/THF	12.3	15.2	50.2	24.6
7	$NaNH_2$	PhMe (O_2 free)	0.5	0.8	91.2	3.2
8	KHMDS	PhMe/THF (O_2 free)	11.5	13.1	65.4	4.1

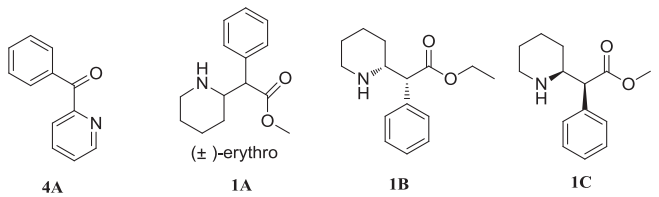


Figure 2. Structure of impurities.

Scheme 2. The mechanism of formation impurity 4A.

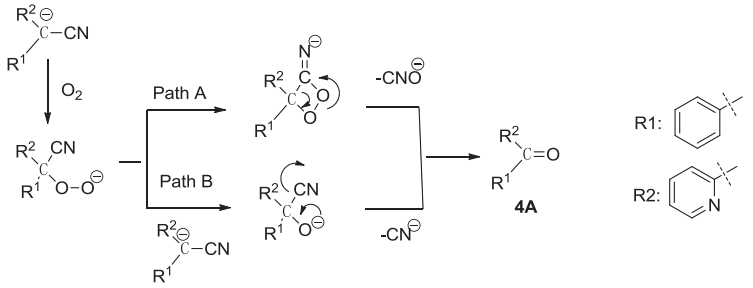


Table 2

Reaction conditions for the hydrogenation step.

Entry	Catalyst	Solvent	Pressure (MPa)	Time (h)	Yield (%)
1	5% Pd/C	AcOH	2	20	Trace
2	5% Pd/C	AcOH/TFA	3	20	Trace
3	10% Pd/C	AcOH	2	4	99[a]
4	10% Pd/C	AcOH/TFA	2	4	90[a]
5	10% Pd/C	MeOH/H_2SO_4	2	4	50[a]
6	10% Pd/C	AcOH	1	20	95[a]
7	10% Pd/C	AcOH	3	3	98[a]

[a]Isolated yield.

Table 3

Resolution of compound 7.

Entry	Resolving agent	Solvent	Crystallization temperature (°C)	ee (%)	Yield (%) [a]
1	D-TA	MeOH	25	85.3	17.5
2	D-DBTA	MeOH	25	98.3	25.2
3	D-DTTA	MeOH	25	95.6	26.3
4	D-DBTA	EtOH	25	97.3	35.0
5	D-DBTA	i-PrOH	25	96.7	45.7
6	D-DBTA	i-PrOH	20	76.4	48.2
7	D-DBTA	i-PrOH	30	99.5	44.4
8	D-DBTA	i-PrOH	35	99.6	40.8

[a]Isolated yield.

45.7% yield (entry 5), but offered less resolution efficiency than methanol. The resolution efficiency was affected by crystallization temperature, too, and the optimal temperature was 30 C (entry 7) with 99.5% enantiomeric excess (ee) and 44.4% yield.

Next, in an esterification reaction, amide **8** was reacted with methanol in the presence of concentrated sulfuric acid to form the free base methyl ester product. This was then reacted with concentrated hydrochloric acid to obtain the desired **1** with 99.50% purity and 99.70% ee. Three major

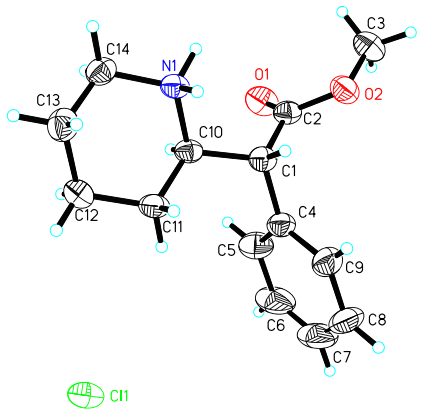


Figure 3. Single crystal X-ray structure of 1. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

impurities in the range of 0.06–0.15% each were separated and characterized as **1A**, **1B**, and **1C** (Fig. 2). **1A**, the *erythro* stereoisomer of **1**, was believed to arise from the process for epimerization of compound **6**. Impurity **1B** is the ethyl ester homologue of compound **1**. It is generally believed that there is small amount of ethanol in methanol, by which the ethyl ester moiety can be introduced as byproduct of the esterification reaction in this step. (*S*)-methyl 2-phenyl-2-((*S*)-piperidin-2-yl)acetate (**1C**) was derived from the resolution of **7**.

The impurities we identified can be removed with the following purification process. The hydrochloric acid salt **1** was recrystallized from water, and this offered a qualified API with 99.92% purity and 99.98% ee and single impurity of less than 0.1%. A single crystal X-ray structure of **1** was obtained (Fig. 3), which confirmed the identity and absolute stereochemistries.

CONCLUSION

An efficient and commercially viable process has been developed for the synthesis of **1** with an overall yield of 23% and ~99.9% purity. The impurities produced in this process were well controlled and removed.

EXPERIMENTAL

Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker NMR AVANCE 400 (400 MHz) spectrometer (Bruker Daltonics Inc., Billerica, MA) with TMS as an internal standard. Chemical shift (d values) and coupling constants (*J* values) are given in ppm and Hz, respectively. ESI mass spectra were performed on an Agilent 6210 TOF spectrometer. Uncorrected melting points were determined on an electrothermal melting point apparatus. Solvents and reagents were used without any pretreatment. Reaction progress and chemical purity were evaluated by HPLC analysis using a Waters Symmetry C18 (Waters, Milford, MA) (5 µm, 250 mm × 4.6 mm)with a mobile phase A (acetonitrile) and B (0.015 mol/L KH_2PO_4), 5:95 → 60:40 v/v; and detection at 220 nm; flow: 1.0 mL/min; temp. 30°C. Chiral purity was evaluated by HPLC analysis using a Daicel Chiralpak AD-H chiral column (5 µm, 250 mm × 4.6 mm) with isocratic mobile phase N-hexane/ethanol/trifluoroacetic acid/diethylamine, 95:5:0.1:0.1 v/v/v/v; and detection at 220 nm; flow: 1.0 mL/min; and temp. 35°C.

2-phenyl-2-(pyridin-2-yl)acetonitrile (4). A 3 L multi-neck glass reactor was charged with toluene (720 mL). In this reaction system, nitrogen purging is required for 0.5 h. Sodium amide powder (138 g, 3.54 mol) was added to this solution at room temperature, then benzyl cyanide (217 g, 1.85 mol) and 2-chloropyridine (200 g, 1.77 mol) were added dropwise successively. The reaction mixture was stirred at the same temperature for 2 h. After cooling to 10°C, the reaction mixture was quenched with water (620 mL). Ethyl acetate (600 mL) was added to the solution, and the organic layer was separated and washed with brine (600 mL). The solvent was removed under reduced pressure, and toluene (100 mL), followed by n-hexane (1.1 L), were added to this residue. The mixture was stirred for 1 h, and filtered. The filter cake was dried under vacuum to afford the desired **4** as a light-yellow solid. This crude product was further purified by recrystallization from ethyl acetate (600 mL) to obtain **4** as a white solid (289 g, 84.2% yield) with 99.10%. Mp 84-86°C; MS *m/z* 195 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.59-8.58 (d, J=4.4Hz, 1H), 7.85-7.81 (dt, J_1=1.6Hz, J_2=7.6Hz, 1H), 7.46-7.45 (m, 3H), 7.42-7.38 (m, 2H), 7.36-7.31 (m, 2H), 5.93 (s, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 155.4, 149.7, 137.9, 135.6, 129.1, 128.2, 127.4, 123.3, 122.4, 119.7, 43.6.

2-phenyl-2-(pyridin-2-yl)acetamide (5). A 5 L multi-neck glass reactor was charged with concentrated sulfuric acid (570 mL). After cooling to 10°C, compound **4** (457 g, 2.36 mol) was added portion-wise, then the mixture was stirred at room temperature for 12 h. The reaction mixture was cooled to 10°C, water (1.7 L) was added dropwise, and adjusted to pH 12 by 30% sodium hydroxide solution. The precipitate was isolated and washed with water (200 mL). The filter cake was dried under vacuum to afford **5** as a light-yellow solid (478 g, 95.8% yield). Mp 134-135°C; MS *m/z* 213 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49-8.48 (d, J=4.4Hz, 1H), 7.76 (br, 1H), 7.74-7.69 (dt, J_1=1.6Hz, J_2=7.6Hz, 1H), 7.38-7.36 (m, 3H), 7.33-7.30 (m, 2H), 7.26-7.22 (m, 2H), 7.16 (br, 1H), 5.09 (s, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 172.3, 159.6, 148.8, 139.3, 136.6, 128.7, 128.3, 126.8, 123.0, 122.0, 59.3.

(±)-*erythro*/*threo*-2-phenyl-2-(piperidin-2-yl)acetamide (6). A 5 L hydrogenation reactor was charged with Pd/C (10% Pd content, 20 g), AcOH (2.4 L) and compound **5** (220 g, 1.04 mol). The reactor was pressurized with hydrogen (2 MPa) and then heated to 70°C for 10 h. The reaction mixture was filtered to remove catalyst, and the solvent was concentrated under reduced pressure (~30 mmHg). Water (1.9 L) was added to this residue, the mixture was cooled to 10°C, and adjusted to pH 12 with a 30% sodium hydroxide solution. The precipitate was isolated and washed with water (100 mL). The filter cake was dried under vacuum to afford **6** as a white solid (223 g, 99.5% yield). Mp 156-157°C; MS *m/z* 219 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.37-7.21 (m, 5H), 3.28-3.26 (d, J = 10.0Hz, 1H), 2.97-2.93 (t, J = 9.6Hz, 1H), 2.77-2.74 (d, J = 10.8Hz, 1H), 2.36-2.31 (m, 1H), 1.70-1.67 (d, J = 9.2Hz, 2H), 1.42 (m, 1H), 1.28-1.24 (m, 2H), 1.14-1.06 (q, J = 11.2Hz, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 175.3, 139.2, 128.9, 128.6, 127.1, 58.9, 58.1, 46.3, 29.6, 26.2, 24.3.

(±)-*threo*-2-phenyl-2-(piperidin-2-yl)acetamide (7). A 10 L multi-neck glass reactor was charged with **6** (200 g, 0.91 mol), potassium tert-butoxide (205 g, 1.83 mol), and toluene (6 L) under a nitrogen atmosphere. The reaction mixture was heated to 70°C for 6 h. After cooling to 10°C, the reaction mixture was quenched with water (400 mL). Then, 5 N hydrochloric acid (2.4 L) was added dropwise and stirred for another 1 h. The water layer was separated and adjusted to pH 12 using 30% sodium hydroxide solution. The precipitate was isolated and washed with water (100 mL). The filter cake was dried under vacuum to afford **7** as a light-yellow solid (165 g, 82.5% yield). Mp 173-174°C; MS *m/z* 219 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.28-7.21 (m, 5H), 3.28-3.25 (d, J = 9.6Hz, 1H), 2.97-2.89 (m, 2H), 2.45 (m, 1H), 1.58-1.55 (m, 1H), 1.45-1.42 (m, 1H), 1.27-1.24 (m, 1H), 1.13-1.07 (m, 2H), 0.87-0.84 (m, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 173.6, 138.5, 128.5, 128.1, 126.5, 58.1, 57.8, 46.1, 29.5, 25.7, 24.1.

(R)-2-phenyl-2-((R)-piperidin-2-yl)acetamide (8). A 5 L multi-neck glass reactor was charged with **7** (100 g, 0.46 mol), D-DBTA (164.2 g, 0.46 mol), and isopropanol (3.2 L), heated to 60°C for 0.5 h. After cooling to 30°C, the precipitate was isolated to afford a light-yellow solid. This solid was crystallized from isopropanol (600 mL) and dried under vacuum to afford a white solid. The white solid was added to 6 N hydrochloric acid (330 mL), and stirred for 4 h. The mixture was filtered, and the filtrate was cooled to 10°C, and adjusted to pH 12 using 30% sodium hydroxide solution. The precipitate was isolated and washed with water (100 mL). The filter cake was dried under vacuum to afford **8** as a white solid (44.4 g, 44.4% yield). Mp 175-176°C; MS *m/z* 219 $[M+H]^+$. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O) δ 7.53 (br, 1H), 7.29-7.21 (m, 5H), 6.86 (br, 1H), 3.26-3.24 (d, J = 9.6Hz, 1H), 2.96-2.92 (m, 2H), 2.46 (m, 1H), 1.84 (br, 1H), 1.59-1.56 (J = 12.0Hz, 1H), 1.46-1.43 (J = 12.0Hz, 1H), 1.28-1.22 (m, 1H), 1.19-1.07 (m, 2H), 0.87-0.79 (m, 1H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 174.1, 138.8, 128.4, 128.2, 126.7, 58.5, 58.1, 46.4, 29.8, 25.9, 24.2.

(R)-methyl 2-phenyl-2-((R)-piperidin-2-yl)acetate hydrochloride (1). A 5 L multi-neck glass reactor was charged with **8** (100 g, 0.46 mol), concentrated sulfuric acid (130 mL), and methanol (1.1 L), and heated to 65°C for 40 h. The reaction mixture was cooled to room temperature, and the solvent was concentrated under reduced pressure (~30 mmHg). Water (800 mL) and isobutyl acetate (1.5 L) were added to this residue. The mixture was cooled to 10°C, and adjusted to pH 12 using 30% sodium hydroxide solution. The organic layer was separated and dried with anhydrous magnesium sulfate, and the solution was filtered. Concentrated hydrochloric acid (38 mL) was added to this filtrate, and stirred for 2 h. The precipitate was isolated and washed with isobutyl acetate (100 mL). The filter cake was dried under vacuum to afford **1** as a white solid (107.6 g, 87.3% yield) with 99.50% purity and 99.70% ee.

The crude product (107.6 g, 0.4 mol) was further purified by recrystallization from pure water (100 mL) to obtain the qualified product **1** (98.3 g, 91.4% yield) with 99.92 purity and 99.98% ee. $[\alpha]_D^{25}$ +85.6 (MeOH, *c* 1) (lit [4b]. $[\alpha]_D^{25}$ +84 (MeOH, *c* 1)); Mp 222-223 C (lit [4b]. Mp 222–224°C); MS *m/z* 234 $[M+H]^+$. ^{1}H NMR (400Hz, DMSO-d_6) δ ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (br, 1H), 8.97 (br, 1H), 7.41-7.26 (m, 5H), 4.18-4.16 (d, J = 9.2Hz, 1H), 3.77-3.75 (m, 1H), 3.66 (s, 3H), 3.25 (m, 1H), 2.94 (m, 1H), 1.67-1.64 (m, 3H), 1.41-1.25 (m, 3H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 171.3, 134.2, 129.1, 128.6, 128.2, 56.8, 53.3, 52.6, 44.5, 25.7, 21.5, 21.4.

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